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First Evidence of Endo-Epicardial Asynchrony of the Left Atrial Wall in Humans

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ABSTRACT

Asynchronous activation of the endo-epicardium plays an important role in persistence of atrial fibrillation. So far, endo-epicardial asynchrony has only been demonstrated in the human right atrium. Our data provides the first evidence for existence of a considerable degree of endo-epicardial asynchrony in the human left atrium. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2020;2:745-9) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Atrial fibrillation (AF) is regarded as the cardiovascular epidemic of the 21st century. It is a progressive disease which is associated with serious complications such as stroke, heart failure and increased mortality. However, treatment of AF is still suboptimal as mechanisms underlying AF initiation and persistence are still incompletely understood (1).

Simultaneous endo-epicardial mapping provides novel insights into the arrhythmogenic substrate underlying AF (2-4). It was recently discovered that persistence of AF is caused by asynchronous electrical activation of adjacent endo-epicardial layers, referred to as endo-epicardial asynchrony (EEA) of the right atrial (RA) wall (2). This phenomenon may even present during sinus rhythm (SR) (3). The existence of EEA is a prerequisite for transmural conduction, giving rise to so-called focal waves in the opposite layer. It is assumed that over time, enhanced by AF-induced structural remodeling, the electrical syncytium of atrial myocytes becomes disrupted and that the atrial wall is gradually transformed into layers of narrow, anatomically delineated pathways. Based on these findings, it is postulated that progression of AF transforms the atrial wall into electrical layers in which dissociated waves constantly "feed" each other (2,5).

So far, EEA has been demonstrated only in the human RA, especially in thicker parts. It is understandable that EEA occurs in thicker, trabeculated

LEARNING OBJECTIVES

- Endo-epicardial asynchrony plays an important role in the pathophysiology of atrial fibrillation and may occur in both right- and left atria.
- Simultaneous endo-epicardial mapping may provide more insights into the arrhythmogenic substrate of atrial fibrillation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CB = conduction block

CD = conduction delay

EEA = endo-epicardial asynchrony

IED = interelectrode distance

LA = left atrium

LAA = left atrial appendage

RA = right atrium

parts of the RA free wall (3,6,7). However, whether EEA is also present in the thin lateral wall of the left human atrium (LA) is unknown. The goal of the present study was to investigate if and to what extent EEA also exists in the LA in patients with AF.

METHODS

STUDY POPULATION. Patients (3 males; 73.3 ± 1.5 years of age) with paroxysmal AF undergoing cardiac surgery for coronary artery or valvular heart disease including LA appendage (LAA) amputation were investigated; clinical characteristics are provided in **Table 1**. The mapping protocol was approved by the institutional ethical committee (MEC2010-054).

INVESTIGATIONS AND MANAGEMENT. After the operator performed arterial cannulation, simultaneous endo-epicardial mapping was carried out using a high-density mapping device containing 2 electrode arrays of 8 × 16 electrodes (n = 256; diameter = 0.4 mm, at an interelectrode distance [IED] of 2 mm), positioned exactly opposite each other. Recordings were sampled at a rate of 1 kHz and amplified (gain: 1,000), filtered (bandwidth: 0.5 to 400 Hz), and converted from analog to digital signals (16 bits).

Before extracorporeal circulation in the patient was begun, the mapping device was introduced through the LAA incision and closed with a purse-string suture. The mapping device was positioned with its tip toward the left superior pulmonary vein in order to perform 10 s of SR mapping (**Figure 1**).

DATA ANALYSIS. Unipolar electrograms were analyzed semiautomatically using custom-made Python version 3.6 software (Arlington, Virginia). Local activation times were determined by marking the steepest negative slope of atrial potentials with a minimal slope of 0.05 mV/ms. Mean activation time was calculated for each patient and each layer separately. Areas of conduction delay (CD) and conduction block (CB) were defined as activation time differences of ≥7ms and ≥12 ms, respectively, between neighboring electrodes. These cutoff values were derived from previous studies and corresponded to effective conduction velocities of 17 to <29 cm/s for CD and <17 cm/s for CB (8,9).

As shown in the right panel of **Figure 1**, local endo-epicardial activation time differences were determined by selecting the median of the time delays within the exact opposite electrode and its 8 surrounding electrodes. The asynchrony map shows the longest time delay for every endo-epicardial electrode pair. In accordance with prior endo-epicardial mapping studies, EEA was defined as a transmural difference in electrical activation of ≥15 ms between 2 opposite electrodes (2,3).

TABLE 1 Patient Characteristics

	Patient I	Patient II	Patient III
Age, yrs	72	73	75
Sex	Male	Male	Male
BMI, kg/m^2	22.8	22.3	29.7
Underlying heart disease	MVD	CAD	CAD
History of AF	PAF	PAF	PAF
Time since AF diagnosis, yrs	4.8	0.03	0.54
LVF	Mildly impaired	Good	Good
LA diameter, mm	49	55	45
LA volume, ml	72	75	57
DM	No	Yes	Yes
Hypertension	No	Yes	Yes

AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; DM = diabetes mellitus; LA = left atrium; LVF = left ventricle function; MVD = mitral valve disease; PAF = paroxysmal atrial fibrillation.

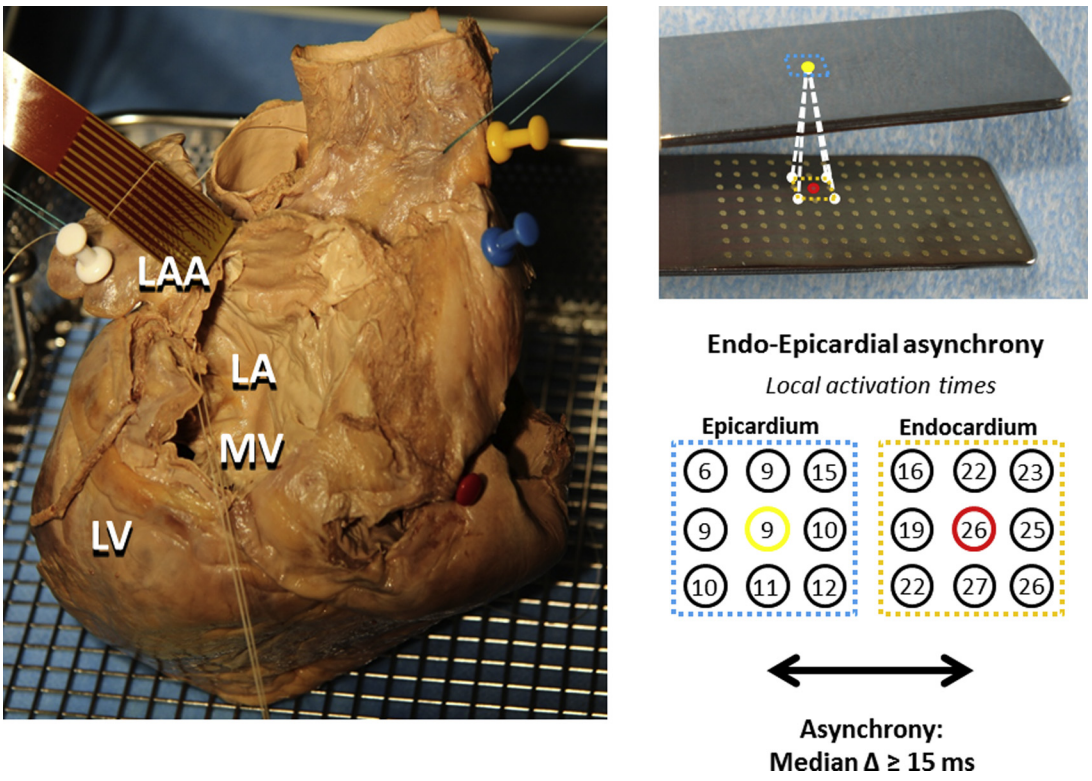
RESULTS

A total of 35 SR beats were analyzed. Mean total activation time of the entire endo-epicardial mapping area was 42.4 ± 9.5 ms and did not differ between both layers (epicardium: 31.2 ± 9.9 ms; and endocardium: 37.8 ± 10.3 ms; p = 0.60). Areas of CD and CB were observed in 3.2% and 6.3%, respectively, at the epicardium and 3.3% and 3.0%, respectively, at the endocardium. The lowest amount of conduction disorder (CD: 5.2%; CB: 0.3%) was observed in the patient who underwent his first AF episode only 11 days prior to surgery. Also, no EEA was present in that patient. In the 2 patients with paroxysmal AF of >6 months, the rates of EEA were 2.7% and 41.4% (degree of EEA [15 to 44 ms]), respectively. Interestingly, the patient with the highest degree of EEA (maximal: 44 ms) had paroxysmal AF for almost 5 years. **Figure 2** shows color-coded activation maps of the endo-epicardium and a corresponding EEA map of 1 single SR beat from that patient.

DISCUSSION

The present data provide evidence for the existence of a significant degree of EEA in the human LA, as well, even during SR. Surprisingly, the degree of EEA in the LA was as high as 44 ms. Assuming a wall thickness of 2 or 3 mm, an EEA of 44 ms would require slow, transmural conduction velocities of 4.5 and 6.8 cm/s, respectively.

FIGURE 1 Pulmonary Veins Are Dissected and the Mitral Valve Is Exposed



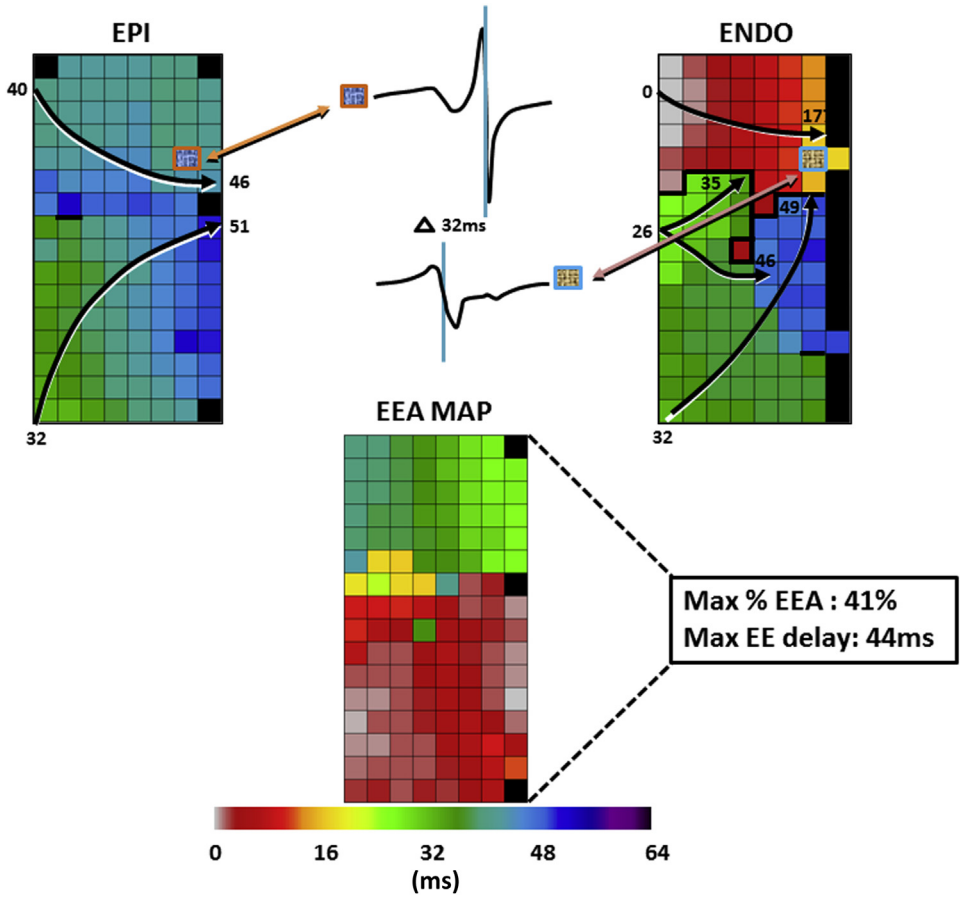
(Left) In the posterior view, pulmonary veins are dissected, and the mitral valve is exposed. The epicardial electrode array is shown on the LAA and points toward the left superior pulmonary vein (virtual in this dissected heart). The endocardial electrode array is not shown in this figure in order to maintain overview. Atrial wall thickness at the mapping location was 2 mm in this heart. **(Right)** In the **upper panel**, the endo-epicardial electrodes are fixed on a flexible spatula. The exact opposite electrodes are marked with a **yellow** and a **red dot**. The surrounding 8 electrodes are marked with **squares**. **(Right)** In the **lower panel**, the local activation times of directly opposite and its 8 surrounding electrodes are shown. Differences in local activation time between the reference electrode and the 9 opposite electrodes were calculated from the endo-epicardium. LA = left atrium; LAA = left atrial appendage; LV = left ventricle; MV = mitral valve.

Derakchan et al. (6) performed simultaneous endo-epicardial contact mapping of both canine atria. A total of 240 unipolar epicardial electrodes (IED = 3.1 to 6 mm) and 128 unipolar endocardial electrodes (IED = 6 to 9 mm; 64 electrodes) were inserted within the atria through an incision in the LAA. During pacing (cycle length: 250 ms) at the right atrial appendage, RA endocardial activation spread faster than RA epicardial activation (respectively: 45 ± 12 ms vs. 60 ± 19 ms; $p < 0.05$). However, this was not the case in the LA. Eckstein et al. (4) performed simultaneous endo-epicardial mapping (IED: 1.6 mm; 146 epicardial and 90 endocardial unipolar electrodes) of the LA free wall in goats during SR, acute AF, after 3 weeks, and after 6 months of AF. Almost no EEA was observed during SR; however, EEA did increase along with duration of AF and occurred at up to 50 ms. EEA occurred more often at thicker parts of the LA. These findings correspond to prior mapping studies examining the RA, which demonstrated that the persistence of AF is also associated with an increase in EEA and focal waves in trabeculated parts of the RA (2,8,9). Eckstein et al. (4) also observed that, with increasing duration of AF (acute AF to 6 months of AF), there was a decrease in LA wall thickness and an increase in EEA. These findings imply that the absolute thickness of the atrial wall together with the degree of electrical and structural remodeling are important for the occurrence of EEA.

CONCLUSIONS

Now it has been demonstrated that a considerable degree of EEA can occur in both the RA and the LA. It

FIGURE 2 Activation Maps of the Epi-Endocardium of 1 SR Beat



Arrows indicate the main direction of the propagating wavefront, and **thick black lines** indicate areas of conduction block. Activation begins in the **upper part** of the endocardial mapping area, and the propagating wavefront is blocked in the middle of the array. The **middle and lower parts** of the mapping area are activated 26 and 32 ms, respectively, later, and within the following 29 ms, the whole mapped epicardial area is activated as well. Two unipolar electrograms recorded from 2 opposite electrodes show a considerable difference of 32 ms in local activation time between both layers. The maximum degree of EEA measured in this patient was 44 ms. The color-coded EEA map in the **lower panel** demonstrates the degree of EEA in a color and shows that EEA is present in 41% of the mapping area. EE= endo-epicardial; EEA = endo-epicardial asynchrony; ENDO = endocardium; EPI = epicardium.

can be assumed that EEA can occur anywhere in both atria. This is in line with prior epicardial mapping studies demonstrating that focal waves, which may arise due to EEA, occurred throughout both atria without predilection sites (10). Although only 3 patients are described, the highest degree of EEA was found in the patient with the longest history of AF. If this observation is confirmed in larger populations, it indicates that even during SR the degree of EEA is indeed related to AF duration and that early intervention is mandatory to prevent progression of AF. Patients with extensive remodeled atria and numerous areas of EEA may not benefit from ablative therapy. Several mapping studies and reports of hybrid procedures have shown that AF consists of a 3-dimensional arrhythmogenic substrate. In the presence of EEA, endocardial mapping alone may not provide sufficient guidance for ablative therapy (2,11). Knowledge of EEA and the ability to stage AF, based on the degree of EEA, is essential for individualized and staged AF therapy.

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